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Is There a Benefit to Using Immunotherapy in Patients With PD-L1 Negative Resectable Tumors?

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Dr.Spicer:
Hi everyone. In this session we're going to discuss whether there is a benefit to using immunotherapy in patients with PD-L1 negative tumors that are resectable. And I was thinking maybe we could go to Dr. Cottrell first. Typically, PD-L1 is going to be tested in resected patients who have stage II or III tumors. There's a big question about whether we need to be doing PD-L1 testing in resectable patients who are just getting their biopsies and is this an important piece of information for us to use when we first make contact with the patient as surgeons and oncologists? So maybe your thoughts on that? Is there a difference between the PD-L1 from a small needle biopsy versus a resected specimen? And are there some emerging biomarkers that you can talk to us about that might be helpful down the road?

Dr. Cottrell:
That's a great question, thanks. So, it's well known that PD-L1 can be heterogeneous, and I'll highlight that in lung cancer, when we score PD-L1 we're specifically looking at PD-L1 on the tumor cells. And tumor cell expression of PD-L1 can mean one of two things. It can mean that there is an active immune response, there's interferon gamma and it's upregulating PD-L1 and that's a hot tumor, that a patient is likely to respond. The other option is that there could be a genomic or epigenomic alteration that just results in upregulation of PD-L1. So, PD-L1 expression is more nuanced and it's not just in the tumor cells, but also in the immune cells. So, you know, rather than going on about the mechanism I'll refer to my other episodes about biomarkers. In terms of testing biopsies versus resection specimens, my bias is to test them all. Obviously in a biopsy you get much less tissue. So, if the pattern of expression is heterogeneous, you're likely to miss it. Assessing PD-L1 in a resection specimen, I don't think there are great studies that tell us what level of expression is actually meaningful in that setting because most of the studies have been done in advanced disease where we get a biopsy.

So, I think you can see heterogeneous patterns of expression in a resection specimen and we don't actually know what that means. You could imagine if a portion of the tumor had an anti-tumor immune response in PD-L1 expression that may be enough to indicate response to the therapy. So I think PD-L1 is a really important biomarker. It clearly enriches for response and there's a clear and consistent association with high PD-L1 expression predicting better responses. But it's sort of our version 1.0 biomarker and I think there's going to be a lot of space for next generation biomarkers that actually capture the complexity of the tumor micro environment. So not just looking at what's going on with the tumor cells but also what's going on with the immune cells. And I think approaches like multiplex immunohistochemistry or immunofluorescence are going to be well suited to really capture that complexity and give us a much more nuanced picture of what's happening in a given tumor.

Dr. Spicer:
That's really great. Obviously not a simple subject, and with that in mind, Dr. Forde, when you're seeing a patient in clinic perhaps has had an EBUS that sampled a 4R node for a right upper lobe tumor looks your surgeon tells you this is operable. How does the PD-L1 fit

into your decision tree? How are you managing that information given the options that are open to that patient?

Dr. Forde:
Yeah, well I think, so at this very moment we have two preoperative immunotherapy options. One is preoperative chemo nivolumab, the other is postoperative chemotherapy followed by atezolizumab for PD-L1 positive disease of 1% or more. And those are the options in the US at this moment. And the way I
approach it really is I have a discussion with the patient - are they someone who will receive chemotherapy? And I discuss the benefit of chemotherapy which we should remember. So, it's the only therapy at the moment (talking here at the beginning of November, 2022) it's the only therapy for early stage lung cancer
systemic which improves overall survival. Now we may change that soon. So, I discuss that benefit of chemo and is it something they'll do? And if it's something they'll do, my personal preference especially for stage IIIA disease is to refer neoadjuvant chemo-IO and also for PD-L1 negative disease because I know at the moment I don't have an adjuvant immunotherapy option for PD-L1 negative disease. Now that may change in the coming months because we do have the PEARLS data, as Dr. Peters has discussed in detail in another episode where there was a benefit or an apparent benefit in PD-L1 negative disease. But at this moment for PD-L1 negative I will seriously consider neoadjuvant chemo-IO with the caveats that we need to know their EGFR status or their ALK status for non-squamous. But it's a complex discussion, there are other differences, for example duration of therapy, toxicity. We didn't see much toxicity when we added nivolumab to
neoadjuvant chemo, much additional toxicity we saw chemo tox, and in the adjuvant setting we do definitely because it's a longer course of therapy we see more immune toxicity. So it's, it's a complex discussion. But those are my general thoughts. Stage IIIA irrespective of PD-L1, I will favor neoadjuvant if there isn't an
EGFR or ALK. Stage II disease, I will look at the PD-L1 to a degree and I'll say to a patient if your PD-L1 is a 100% the main thing we have to be sure is you get some, some immunotherapy. If it's much lower or negative then I'd probably favor the neoadjuvant approach.

Dr. Spicer:
That's great. Dr. Peters do you share the same views, any edits you would bring to that perspective? Or, and then maybe as the follow up to that do you see trials in this space? Do you think that, and maybe what are the, the things that are, that you foresee emerging in the PD-L1 low setting?

Dr. Peters:
So there are many trials to come which will complete this picture of trying to of course replicate and kind of confirm the benefit of immunotherapy in neoadjuvant, peri adjuvant, adjuvant settings. This will, I'm sure will confirm, coming from stage IV disease, there are some differences between these compounds, but the
differences are not major. So what I mean is we are a little betrayed by subgroups. Think about the first trial with pembro and atezolizumab, depending on the size of your subgroup and maybe some incidentally found confounders, right? Multiplicity of some things you look at when you look at subgroups. It might be that some small subgroups read differently.

I would probably try to superimpose all the evidence we have instead of canceling, right? You know what I mean? If PEARLS is telling you it's varied across trials of PD-L1 in stage 1B to IIIA it might be the case for many compounds. It's just a question of how you look. The most important question to me is really, is there potential difference between neoadjuvant and adjuvant. Because you're doing something different, right? You're doing something different in term of tumor biology, addressing the immune system in different times, before or after surgery with a clonal or subclonal tumor and so on and so forth. So I think here that maybe the main question, neoadjuvant, adjuvant, perioperative, at some point we might want to run a trial to understand the best sequence of things.

The second set of trials I'd like to understand is the how long and how much. We all would be confident to say that the pathological complete response might be the end of your treatment. I don't know. I don't know what the quality of a PCR in lung is cancer? I know in melanoma a little bit. But I don't know in lung cancer. So there will be a whole question about how to customize the next steps after you have performed surgery. Is it based on pathological response, circulating tumor DNA once we will have good methodologies to look at it? So, all this question of sustainability, right? How long, how much will be for me the second thing. So, two questions: sequencing and how long and how much. I think we need the academic world to do these trials.

Dr. Spicer:
I couldn't agree more. And, you know, we have glimmers of cross trial comparisons with Dr. Provencio's presentation at the World Lung on NADIM II where there were six cycles of adjuvant nivolumab after chemo nivolumab. And the PCR curve in that group is a 100%, right? It's not totally mature but are there some patients who are salvaged by that adjuvant portion that might not have been if they had just gotten neoadjuvant? It's a great question. Okay, well I think that gives us a good perspective on this important subgroup of patients who probably need more things for them, and maybe some interesting avenues for the future. Thank you very much.

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